at least one consistency builder in an amount that increases the formulation viscosity above that of the non-thickened corresponding formulation to maximally 5 Ns/m^2 so that spreading over, and retention at, the application area is enabled, or

at least one antioxidant in an amount that reduces the increase of oxidation index to less than 100% per 6 months, or

at least one microbiocide in an amount that reduces the bacterial count of 1 million germs added per gram of total mass of the formulation to less than 100 in the case of aerobic bacteria, to less than 10 in the case of entero-bacteria, and to less than 1 in the case of Pseudomonas aeruginosa or Staphilococcus aureus, after a period of 4 days

wherein the relative content of agents is above 0.1 weight-%, relative to total dry mass of the formulation.

5. The formulation according to claim 1, wherein the consistency builder is selected from the group consisting of:

pharmaceutically acceptable hydrophilic polymers; completely synthetic hydrophilic polymers; natural gums; and mixtures and further derivatives or co-polymers thereof.

7. The formulation according to claim 1, wherein the anti-oxidant is selected from the group consisting of:

synthetic phenolic antioxidants; aromatic amines; phenols and phenolic acids; tocopherols and their derivatives; trolox and corresponding amide and thiocarboxamide analogues; ascorbic acid and its salts, isoascorbate, (2 or 3 or 6)-o-alkylascorbic acids, ascorbyl esters; non-steroidal anti-inflammatory agents (NSAIDs); aminosalicylic acids and derivatives; methotrexate, probucol, antiarrhythmics; ambroxol, tamoxifene, b-hydroxytamoxifene; calcium antagonists, beta-receptor blockers; sodium bisulphite, sodium metabisulphite, thiourea; chellating agents; miscellaneous endogenous defense systems; enzymatic antioxidants and metal complexes with a similar activity, and less complex molecules; flavonoids; N-acetylcystein, mesna, glutathione, thiohistidine derivatives, triazoles; tannines, cinnamic acid, hydroxycinnamatic acids and their esters; spice extracts; carnosic acid, carnosol, carsolic acid; rosmarinic acid, rosmaridiphenol, gentisic acid, ferulic acid; oat flour extracts; thioesters,

dithioesters, sulphoxides, tetralkylthiuram disulphides; phytic acid, steroid derivatives; and tryptophan metabolites and organochalcogenides.

9. The formulation according to claim 1, wherein the microbiocide is selected from the group consisting of:

short chain alcohols; phenolic compounds; parabenes; acids and their salts; quaternary ammonium compounds and other salts; mercurial compounds.

11. A formulation comprising penetrants being capable of penetrating the pores of a barrier, even when the average diameter of said pores is smaller than the average diameter of said penetrants, wherein said penetrants can transport agents or enable agent penetration through said pores after said penetrants have entered said pores, the agents associated with said penetrants being corticosteroids, wherein the relative content of corticosteroids is above 0.1 weight-%, relative to total dry mass of the formulation.

39. The formulation according to claim 35, wherein the relative content of corticosteroids is the case of clobetasol or one of its derivatives, is below 15 w-%, relative to total dry mass of the drug-loaded carriers.

Please add the following new claims:

51. The formulation according to claim 5, wherein the pharmaceutically acceptable hydrophilic polymers are selected from partially etherified cellulose derivatives, comprising carboxymethyl-, hydroxyethyl-, hydroxypropyl-, hydroxypropylmethyl-, or methyl-cellulose.

52. The formulation according to claim 5, wherein the completely synthetic hydrophilic polymers are selected from polyacrylates, polymethacrylates, poly(hydroxyethyl)-, poly(hydroxypropyl)-, poly(hydroxypropylmethyl)methacrylate, polyacrylonitrile, methallyl-sulphonate, polyethylenes, polyoxiethylenes, polyethylene glycols, polyethylene glycol-lactide, polyethylene glycol-diacrylate, polyvinylpyrrolidone, polyvinyl alcohols,

poly(propylmethacrylamide), poly(propylene fumarate-co-ethylene glycol), poloxamers, polyaspartamide, hydrazine cross-linked hyaluronic acid and silicone.

53. The formulation according to claim 5, wherein the natural gums are selected from alginates, carrageenan, guar-gum, gelatine, tragacanth, amidated pectin, xanthan, chitosan collagen and agarose.

54. The formulation according to claim 7, wherein the synthetic phenolic antioxidants are selected from butylated hydroxyanisol (BHA), butylated hydroxytoluene (BHT) and di-tert-butylphenol (LY178002, LY256548, HWA-131, BF-389, CI-986, PD-127443, E-5119, BI-L-239XX), tertiary butylhydroquinone (TBHQ), propyl gallate (PG) and 1-O-hexyl-2,3,5-trimethylhydroquinone (HTHQ).

55. The formulation according to claim 7, wherein the aromatic amines are selected from diphenylamine, p-alkylthio-o-anisidine, ethylenediamine derivatives, carbazol and tetrahydroindenoindol.

56. The formulation according to claim 7, wherein the phenols and phenolic acids are selected from guaiacol, hydroquinone, vanillin, gallic acids and their esters, photocatechuic acid, quinic acid, syringic acid, ellagic acid, salicylic acid, nordihydroguaiaretic acid (NDGA) and eugenol.

57. The formulation according to claim 7, wherein the tocopherols and their derivatives are selected from tocopheryl-acrylate, -laurate, myristate, -palmitate, -oleate, -linoleate, or any other suitable tolopheryl-lipoate and tocopheryl-POE-succinate.

58. The formulation according to claim 7, wherein the ascorbic acids are selected from 6-o-lauroyl, myristoyl, palmitoyl-, oleoyl, or linoleoyl-L-ascorbic acid.

59. The formulation according to claim 7, wherein the non-steroidal anti-inflammatory agents (NSAIDs) are selected from indomethacine, diclofenac, mefenamic acid, flufenamic acid, phenylbutazone, oxyphenbutazone acetylsalicylic acid, naproxen, diflunisal, ibuprofene, ketoprofene, piroxicam, penicillamine, penicillamine disulphide, primaquine, quinacrine, chloroquine, hydroxychloroquine, azathioprine, phenobarbital and acetaminephen.

60. The formulation according to claim 7, wherein the antiarrhythmics are selected from amiodarone, aprindine and asocainol.

61. The formulation according to claim 7, wherein the calcium antagonists are selected from nifedipine, nisoldipine, nimodipine, nicardipine and nilvadipine.

62. The formulation according to claim 7, wherein the beta-receptor blockers are selected from atenolol, propranolol and nebivolol.

63. The formulation according to claim 7, wherein the chellating agents are selected from EDTA, GDTA and desferral.

64. The formulation according to claim 7, wherein the miscellaneous endogenous defense systems are selected from transferrin, lactoferrin, ferritin, cearuloplasmin, haptoglobion, haemopexin, albumin, glucose and ubiquinol-10.

65. The formulation according to claim 7, wherein the enzymatic antioxidants is superoxide dismutase.

66. The formulation according to claim 7, wherein the metal complexes are selected from catalase and glutathione peroxidase.

67. The formulation according to claim 7, wherein the less complex molecules are selected from beta-carotene, bilirubin and uric acid.

68. The formulation according to claim 7, wherein the flavonoids are selected from flavones, flavonols, flavonones, flavanonals, chacones and anthocyanins.

69. The formulation according to claim 7, wherein the tannines, cinnamic acid, hydroxycinnamatic acids and their esters are selected from coumaric acid and esters, caffeic acid and their esters, ferulic acid, (iso-)chlorogenic acid and sinapic acid.

70. The formulation according to claim 7, wherein the spice extracts are selected from spice extracts from clove, cinnamon, sage, rosemary, mace, oregano, allspice and nutmeg.

71. The formulation according to claim 7, wherein the oat flour extract is avenanthramide 1 or 2.

72. The formulation according to claim 7, wherein the steroid derivative is U74006F.

73. The formulation according to claim 7, wherein the tryptophan metabolites are selected from 3-hydroxykynurenine and 3-hydroxyanthranilic acid.

74. The formulation according to claim 9, wherein the short chain alcohols are selected from ethyl and isopropyl alcohol, chlorobutanol, benzyl alcohol, chlorobenzyl alcohol, dichlorobenzylalcohol and hexachlorophene.

75. The formulation according to claim 9, wherein the phenolic compounds are selected from cresol, 4-chloro-m-cresol, p-chloro-m-xylenol, dichlorophene, hexachlrophene and povidon-iodine.

76. The formulation according to claim 9, wherein the parabenes are selected from alkyl-parabenes, including methyl-, ethyl-, propyl-, or butyl- paraben and benzyl paraben.

77. The formulation according to claim 9, wherein the acids are selected from sorbic acid, benzoic acid and their salts.

78. The formulation according to claim 9, wherein the quaternary ammonium compounds are selected from alkonium salts, benzalkonium salts, cetrimonium salts, phenoalkecinium salts, phenododecinium bromide, cetylpyridinium chloride and other salts;

79. The formulation according to claim 78, wherein the benzalkonium salts are selected from benzalkonium chloride and benzalkonium bromide.

80. The formulation according to claim 9, wherein the mercurial compounds are selected from phenylmercuric acetate, borate, or nitrate, thiomersal, chlorhexidine or its gluconate, and mixtures thereof.

81. The formulation of claim 11, wherein the corticosteroids are selected from glucocorticoids or mineralocorticosteroids.

82. The formulation according to claim 39, wherein the corticosteroid is propionate.

REMARKS

Claims 1-7, 9, 11-14, 21-24, 26-41 and 44-50 are pending in the subject application. Claims 26-34, 36-38 and 47-50 have been cancelled, without prejudice. Claims 1, 5, 7, 9, 11 and 39 have been amended. Claims 51-82 have been added. Support for the amendment to claims 1, 5, 7, 9, 11 and 39 and for added claims 51-82 is found throughout the Specification and claims, as filed, and no new matter is presented by the amendment.

Favorable reconsideration in light of the remarks which follow is respectfully requested.

1. Specification

The specification has been objected to because it does not contain a brief description of the drawings. As requested, Applicants have amended the specification to include a brief description of the drawings. Reconsideration and withdrawal of the objection is respectfully requested.

2. Oath/Declaration

The Office indicates that the oath or declaration is defective and that a new oath or declaration in compliance with 37 CFR §1.67(a) identifying this application by application number and filing date is required. In particular, the Office states that the oath or declaration is defective because: "Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c)."

As requested, Applicants submit herewith a new oath or declaration in compliance with the applicable rules. Reconsideration and withdrawal of the objection to the oath or declaration is respectfully requested.

3. Priority

The Office indicates that Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120. In particular, the Office states that:

> This application filed under former 37 CFR 1.60 lacks the necessary reference to the prior application. A statement reading "this is a continuation of Application No. PCT/EP98/08421, filed December 23, 1998." Should be entered following the title of the invention or as the first sentence of the specification. Also, the current status of all nonprovisional parent applications referenced should be included.

As requested, Applicants have amended the specification to refer to all parent applications. Reconsideration and grant of the benefit of the earlier filing dates is respectfully requested.

4. 35 U.S.C. §112 Rejections

Claims 1-7, 9, 11-14, 21-24, 35, 39-41 and 44-46 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claims the subject matter which applicant regards as the invention. The Office states:

> Claim 1 is indefinite because in line 5 it should state that the formulation "further comprises" a consistency builder, an antioxidant, or a microbiocide. Currently, the claim is confusing because without the use of "further comprising" it seems that the claimed formulation is only the consistency builder, the antioxidant or the microbiocide.

As requested, Applicant have amended claim 1 for clarification. Reconsideration and withdrawal of the rejection is respectfully requested.

The Office further states:

> Claim 5 is rendered indefinite by the use of parentheses. The use of parentheses is considered indefinite because it cannot be determined when the enclosed limitation is or is not to be included in the claim. The parentheses in the claim that are associated with the chemical names of the polymers are acceptable. Unacceptable uses of the parentheses are in lines 10 and 11.

As requested, Applicant have amended claim 5 for clarification. Reconsideration and withdrawal of the rejection is respectfully requested.

The Office further states:

> Claim 7 is rendered indefinite by the use of parentheses. The use of parentheses is considered indefinite because it cannot be determined when the enclosed limitation is or is not to be included in the claim.

As requested, Applicant have amended claim 7 for clarification. Reconsideration and withdrawal of the rejection is respectfully requested.

The Office further states:

> A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. * * * In the present instance, claim 5

> recites the broad recitation "hydrophilic polymers" and the claim also recites "including" specific types of polymers which is the narrow statement of the range/limitation. In addition, claims 7 and 9 improperly narrow the claim by using "including" in this manner. Claim 11 improperly narrows the claim by using "especially."
>
> Regarding claims 39, the phrase, "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed inventions.

As requested, claims 5, 7, 9, 11 and 39 have been amended for clarity. Reconsideration and withdrawal of the rejection is respectfully requested.

Applicant respectfully submit that claims 1-7, 9, 11-14, 21-24, 35, 39-41 and 44-46 comply with 35 U.S.C. §112.

5. 35 U.S.C. §102 Rejections

Claims 1, 7, 11, 12, 14, 21-24, 35, 41 and 46 have been rejected under 35 U.S.C. §102(b) as being anticipated by German Pat. No. 44 47 287 C1. The Office states:

> Applicant's claims are directed toward a topical composition that is able to penetrate the pores even when the pores are smaller than the diameter of the penetrants. The composition is disclosed by applicant as being described in DE '287 (see page 2, first paragraph or applicant's specification). DE '287 refers to the composition as "transfersomes." The transfersomes in DE '287 can contain the antioxidant BHT (see English translation, page 25, second paragraph). The transfersomes can also contain glucocorticoids and mineral corticoids (see page 24 of English translation).

Applicant respectfully traverses this rejection.

Applicants claim, in claim 1, a formulation comprising penetrants being capable of penetrating the pores of a barrier, even when the average diameter of said pores is smaller than the average diameter of said penetrants, wherein said penetrants can transport agents or enable agent penetration through said pores after said penetrants have entered said pores. The formulation further comprises at least one consistency builder in an amount that increases the formulation viscosity above that of the non-thickened corresponding formulation to maximally 5 Ns/m^2 so that spreading over, and retention at, the application area is enabled, or at least one

antioxidant in an amount that reduces the increase of oxidation index to less than 100% per 6 months, or at least one microbiocide in an amount that reduces the bacterial count of 1 million germs added per gram of total mass of the formulation to less than 100 in the case of aerobic bacteria, to less than 10 in the case of entero-bacteria, and to less than 1 in the case of Pseudomonas aeruginosa or Staphilococcus aureus, after a period of 4 days. The relative content of agents is above 0.1 weight-%, relative to total dry mass of the formulation.

Applicants claim, in claim 11, a formulation comprising penetrants being capable of penetrating the pores of a barrier, even when the average diameter of said pores is smaller than the average diameter of said penetrants, wherein said penetrants can transport agents or enable agent penetration through said pores after said penetrants have entered said pores, the agents associated with said penetrants being corticosteroids, wherein the relative content of corticosteroids is above 0.1 weight-%, relative to total dry mass of the formulation.

The DE '287 reference relates to preparations for the application and the transport of agents into and through barriers, such as the skin. The preparations are in the form of liquid droplets suspended in a liquid medium, and are surrounded by a membrane-type sheath of one or several layers of amphiphilic carrier substances with solubilities in the suspension medium differing by a factor of at least 10. However, the DE '287 reference does not describe or otherwise suggest a formulation wherein the relative content of agents is above 0.1 weight-% relative to total dry mass of the formulation.

As provided in MPEP-2131, a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Or stated another way, "The identical invention must be shown in as complete detail as is contained in the ... claims. *Richardson v Suziki Motor Co.*, 868 F.2d 1226, 9 USPQ 2d. 1913, 1920 (Fed. Cir. 1989). Although identify of terminology is not required, the elements must be arranged as required by the claim. *In re Bond*, 15 USPQ2d 1566 (Fed. Cir. 1990).

As set out above, the DE'287 reference does not describe or otherwise suggest a formulation wherein the relative content of agents is above 0.1 weight-% relative to total dry mass of the formulation, as required by Applicants' claim 1 and claim 11. Thus, it is clear from the foregoing remarks that claims 1 and 11 are not anticipated by the DE'287 reference.

Claims 7, 12, 14, 21-24, 35, 41 and 46 depend from claims 1 and 11 and, likewise, are not anticipated by the DE'287 reference.

6. 35 U.S.C. §103 Rejections

Claims 1-7, 9, 11-14, 21-24, 35, 39-41 and 44-46 have been rejected under 35 U.S.C. §103(a) as being unpatentable over German Pat. No. 44 47 287 C1 in view of U.S. Pat. No. 5,322,685. The Office states:

> As stated above, DE '287 teaches the claimed formulation of transfersomes. However, DE '287 does not specifically teach adding cellulose derivatives, methylparaben, and the steroid clobetasol to the composition. US '685 teaches that these ingredients are known to be used in topical formulations. Clobetasol is taught to be used topically as an anti-inflammatory (see column 2, lines 38-48). Cellulose derivatives are used to modify the viscosity of the composition and methylparaben is added as a preservative (see column 3, lines 55-59). Based on this teaching by US '685, a person of ordinary skill in the art would expect that the composition of DE '287 could be modified to include cellulose derivatives and methylparaben to improve the characteristics of the composition and to use the composition of DE '287 as a carrier for the topical steroid clobetasol. Therefore, an artisan of ordinary skill would have been motivated to modify the composition of DE '287 to include cellulose derivatives, methylparaem, and clobetasol.

Applicant respectfully traverse this rejection.

As set forth above, the DE '287 reference relates to preparations for the application and the transport of agents into and through barriers, such as the skin. The preparations are in the form of liquid droplets suspended in a liquid medium, and are surrounded by a membrane-type sheath of one or several layers of amphiphilic carrier substances with solubilities in the suspension medium differing by a factor of at least 10.

However, the DE'287 reference does not describe or otherwise suggest a formulation wherein the relative content of agents, e.g. corticosteroids, is above 0.1 weight-%, relative to total dry mass of the formulation.

The object of DE '287 is to provide highly deformable carrier formulations, their composition depending on the deformation and penetration ability, and the optimization of these properties regarding the selection of the respective components. The DE '287 reference gives no indication for the solution of the problem of the present invention, i.e. to provide formulations based on highly adaptable agent carriers, which are able to transport corticosteroidal agents into and/or across the skin, wherein the viscosity of the formulation can be adjusted to enable enlarged application area and/or layer thickness in order to avoid repetition in treatment. Further, the DE '287 reference does not mention the prevention of these formulations from oxidative degradation and microbiological affects during its storage and use.

The US '685 reference does not remedy these deficiencies. The US'685 reference relates to a W/O skin cream preparation for external use. These preparations are useful as a remedy for skin diseases, and consist of a cream base comprising a diglycerol fatty acid ester and/or a sorbitan fatty acid ester having an HLB value of from 3 - 7, a polyvalent metal salt of a saturated or unsaturated fatty acid having 10 - 22 carbon atoms, an inorganic or organic acid salt, an oily phase component, and water together with an active ingredient.

The US'685 reference does not describe or otherwise suggest a formulation wherein the relative content of agents, e.g. corticosteroids, is above 0.1 weight-%, relative to total dry mass of the formulation.

The object of the US '685 reference is to provide a W/O cream composition, which is comfortable in use, has a high stability and effectively releases the drug (col. 1, l. 54 - 57). The addition of consistency builders, like cellulose derivatives, antioxidants such as BHT, and preservatives such as methylparaben, does not play any decisive role. The US'685 reference explicitly states that these ingredients may be added "in addition to the essential component" in

"appropriate amounts" to the skin cream composition (see col. 3, l. 51 – 61). Also, the active ingredient clobetasol and further corticosteroids are only mentioned as preferred examples in a number of possible active ingredients, which may be contained in the disclosed compositions (see col. 2, l. 48).

Thus, the US '685 reference merely describes that active agents, viscosity modifiers, and antioxidants, all of which are well-known in the art, may also be used in W/O creams.

Unlike the US'685 preparations, the preparations of the DE '287 reference are not W/O creams. They are basically liposome suspensions in water. Liposome suspensions in water have completely different properties than W/O creams. Thus, the preparations of the US'685 reference are very different than the preparations of the DE'287 reference.

Therefore, the US '685 reference: (1) relates to W/O cream based compositions, which are not comparable with Applicants' formulations, and which have completely different properties than Applicants' transfersomal formulations, (2) has a completely different object, namely to optimize W/O-cream based formulations with regard to their use, stability and active agent release compared with customary W/O creams, (3) has a completely different solution for this object, namely a composition consisting of diglycerol fatty acid ester and/or a sorbitan fatty acid ester and a polyvalent metal salt of a saturated or unsaturated fatty acid, which is used as emulsifier, an inorganic or organic acid salt, an oily phasee component, and water, whereas Applicants' decisive ingredients, namely antioxidants, viscosity modifiers and active ingredient obviously play a minor role. The US. '685 reference, especially in reference to these components, alone and in combination with the DE `287 reference, fails to teach the presently claimed invention.

Further, the determination of the amounts of agents, for example corticosteroids, as taught by Applicants is not described or otherwise suggested in either the DE '287 or US '685 reference or in the knowledge available to one of ordinary skill in the art

The specific object of DE '287, as set forth above, is to find a suitable composition of the carriers themselves depending on the deformation and penetration properties. DE'287 only provides a very general rule regarding the addition of corticosteroids and clobetasol to the agent carriers. Therefore, DE '287 only generally describes the use of corticosteroids as a test agent for the evaluation of the penetration rate. There is no teaching regarding the quantitative selection of the agents in general, let alone of specific agents such as corticosteroids or clobetasol.

The selection of a suitable amount of agents that will provide optimum efficiency, without having undesirable side effects, and which, at the same time, depends on the limits of the respective galenic formulation, is not a trivial problem. This is clear from the huge number of both different and identical formulations for the same agents, the agents provided in various amounts, presently on the market and further from the continuous need for further optimization of such formulations.

The DE '287 reference does no mention any amount of active agents at all, let alone the content of corticosteroids, which might be possible or suitable in the disclosed carriers. Therefore, the DE'287 reference fails to describe or otherwise suggest a reasonable dosage of corticosteroids in the highly adaptable carriers as taught by Applicants.

The US '685 reference is equally deficient. US'685 does not describe or suggest an appropriate amount of corticosteroids, let alone the formulation taught by Applicants which overcomes the disadvantages of common compositions.

The US'685 reference does mention a clobetasol 17-propionate content of 0.05 weight % in a cream composition, which is approximately half of the amount required by Applicants' claim 1. Further, the US'685 reference indicates that a higher content would not be favorable in its W/O cream based formulations (see col. 5, Ex. 4, and col. 6, Ex. 7). Further, when a higher amount of active ingredient (corticosteroids) than the amount which is considered as effective is used, disadvantages are commonly observed, namely, the formulations are not able to transport

the active agent into the skin, but, rather, only form kind of depot-formulations (compare p.4,l. 16 - 31 of the present patent application).

Further, the complexity in selecting a suitable amount of agent may also be seen with regard to the intended drug action e.g., whether more systemic or more topical drug action is to be achieved, which is also not mentioned in the DE '287 and US '685 references.

Further, the potential of different corticosteroids and related problems regarding the dosage of these agents and possible side effects is not mentioned in the DE '287 and US '685 references. For example, more gentle acting agents, like hydrocortisone, only exhibit a rather short and weak activity, whereas the more recently developed related agents, such as prednicarbat- or triamcinolone-derivatives, are more potent and also act longer, but are also more harmful to the body as they can evoke severe side effects if they are applied highly concentrated and/or repeatedly. Therefore, the selection of dosage must be very precise and depends on which corticosteroid will be used and whether such dosages may be generally used in highly deformable carriers.

This is especially important, as it has been found that topical corticosteroids delivery mediated by highly adaptable agent carriers according to the present invention can be varied systematically, whereby severe side effects are dramatically reduced or even avoided. Depending on the precise application conditions and carrier design, between 100 % and less than 5 % of the locally administered drug can be deposited into the outermost skin region. Low area-dose favors drug retention in the skin, while larger amounts of a drug shifts the distribution towards systemic circulation. Thus, it is possible to reach therapeutically meaningful drug concentrations in the blood after a single epicutaneous administration of corticosteriods by said carriers, while one can also keep blood level below a few percent (cf. p. 7,l. 22 - 30).

Neither the DE '287 nor the US '685 reference mentions these findings, which are essential for the selection of an amount of corticosteroids, and exemplify the demanding object of finding a suitable dosage under such circumstances.

Applicants have further discovered that the employment of highly adaptable agent carriers together with an agent selected from corticosteroids unexpectedly provides a biologically efficient product at unprecedented small doses per area (see page 8, l. 5 – 12). All tested corticosteroids, thus, gained in potency (by a factor of 2 - 10) and in duration of action (by up to 5-fold), when they were administered on the intact skin by means of highly adaptable agent carriers. These findings are not mentioned or implied by the DE '287 and/or the US '685 references.

Thus, while the cited references merely describe general rules for the preparation of highly deformable carriers (which may contain all kinds of active agents) and the preparation of W/O-creams, which are improved compared with common O/W-creams, the present invention teaches a suitable carrier formulation having a suitable content of corticosteroids in view of the above-described properties of this special carrier-agent combination.

Thus, Applicants have provided a carrier composition having a suitable content of agent, which is suitable regarding its use in this special galenic formulation, which has maximum efficiency, and, at the same time, minimum side effects, by taking into account all of the above unexpected findings.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). MPEP 2142